

# Comparing the effects of shallomin lotion and cryotherapy on treating plane warts

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## ABSTRACT

**Background:** Wart is a common transferable skin disease that is caused by human papilloma virus. Choosing the best treatment method can vary based on age, therapeutic goal, complications, and wart place. Due to antibacterial effect of shallomin (*hirtifolium* Boiss extract) and since its effect has not been studied yet, it was compared to cryotherapy therapeutic methods for treating patients with plane warts. **Methods:** The present study was a randomized clinical trial that was carried out on 40 patients. Sampling was conducted simply by 4 block randomization method. The selected patients were assigned into two Groups of A and B. Data analysis was conducted by descriptive methods, and then, statistical tests including Chi-square, Fisher's exact test, and *t*-test were run to determine the relationship between qualitative and quantitative variables. In so doing, SPSS software version 16.0 was utilized. **Results:** Comparing the means showed that as opposed to cryotherapy, shallomin could not lead to a significant decrease in the size and number of warts. **Conclusion:** According to the results of this study, which is the first and the only investigation into the effects of shallomin on treating plane warts, it can be stated that despite of its antibacterial, antifungal, and anti-herpetic properties, shallamin cannot be a clinically effective option for treating plane warts.

**Keywords:** Cryotherapy, dermatology, shallomin lotion

## Introduction

Wart is a common transferable skin disease that is caused by human papilloma virus (HPV).<sup>[1]</sup> This disease causes beauty problems in the face through cell proliferation, and will triggers pain and inflammation in the affected areas.<sup>[2]</sup> Over long periods, warts may grow into large masses that will remain for months or years.<sup>[3]</sup> To aid the pathogenesis, the virus needs live and active epidermis. Moreover, the moisture of the skin is the predisposing factor for the virus to reach epidermal cells. Till date, more than 120 types of this virus have been identified which can cause different types of wart including common warts, plane

warts, anogenital warts, laryngeal papilloma, and oral mucosa.<sup>[1]</sup> Choosing the best treatment method can vary based on age, therapeutic goal, complications, and wart place.<sup>[4]</sup> Since complete recovery, nonreoccurrence of the disease, the effects of proposed treatments on all patients have not been confirmed, none of the treatments are suggested alone as the successful treatment.<sup>[5]</sup> In 2002, center for disease control recommended cryotherapy, trichloroacetic acid, podophyllin, laser surgery, topical cidofovir, electrocautery, retinoids, and salicylic acid as treatments for wart.<sup>[6]</sup> Applying liquid nitrogen (−196) or nitrous oxide on warts causes dermal, vascular, and edema damage. Response to cryotherapy can be compared to salicylic acid.<sup>[7]</sup> *Allium hirtifolium* Boiss extract (Persian shallot) is used in traditional medicine in Iran and Mediterranean region.<sup>[8]</sup> Flavonoid active compound with the chemical formula of  $C_{14}H_8O_8$  and the proposed name

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of shallomin is responsible for the antimicrobial properties.<sup>[9]</sup> The results of the *in vitro* study indicated that the raw extract of this plant has antibacterial properties against a variety of Gram-positive and Gram-negative pathogenic bacteria such as *Pseudomonas aeruginosa*.<sup>[10]</sup> Moreover, this extract has fungistatic and fungicidal activities against varieties of fungus including *Saccharomyces cerevisiae*, *Aspergillus*, and *Candida albicans*.<sup>[9]</sup> In their study of antitoxic and antimicrobial effects of shallomin in human, Amin *et al.*<sup>[11]</sup> observed that the proposed doses as opposed to placebo (ethanol) had no side effects. Moreover, in another study conducted on patients with mouth blisters, Pipelzadeh *et al.*<sup>[12]</sup> observed that using shallomin resulted in the disappearance all blister disappearing within 24 h after it had been applied. The results of another study carried out on the same issue showed that the components of *A. hirtifolium* could control tumor cell proliferation. Therefore, *A. hirtifolium* can be an effective medicine in treating wart.<sup>[8]</sup> Antimicrobial effect and easy access to shallomin, on the one hand, and lack of investigations into improving wart, on the other hand, led the researcher to study the effect of cryotherapy and compare it with one of the most common methods to treat patients with plane wart.

## Materials and Methods

The present study was a randomized clinical trial that was carried out on 40 patients who were referred Imam Khomeini Hospital in 2015–2016. According to the study's inclusion criteria, qualified patients with plane wart were randomly selected from among the clients who had referred to the Dermatology Clinic of Ahvaz's Imam Khomeini Hospital after necessary permissions had been received from the Ethics Committee, Ahvaz Jundishapur University of Medical Sciences. The study inclusion criteria were lack of restriction for age and gender, number of the wart more than 3 with a minimum diameter of 15 mm, lack of restriction on the distribution of warts, duration of warts' beginning, or no use of other therapeutic methods. The study exclusion was breastfeeding or pregnant woman, immunocompromised individuals, or any type of generalized dermatitis. Sampling was conducted simply by 4 block randomization method. The selected patients were assigned into two groups of A and B. In the case group (Group A), right warts were treated with cryotherapy and left ones with shallomin, whereas in Group B, right warts were treated with shallomin and ones with cryotherapy. Cryotherapy was applied once every 2 weeks while shallomin was used twice a day. Treatment continued for 6–8 weeks or until warts completely disappeared. All treatments were carried out by an assistant dermatologist. For each patient, the first session was devoted to determining the start time, location, number, and diameter of warts (Form 1), and in next sessions, the initial wart was treated with shallomin. Response to the treatment was evaluated through examining the reduction in the diameter of the initial wart and the number of all warts and photographic comparison. Based on the percentage of disappearance, size reduction, and a number of warts, therapeutic response was defined in three sections: complete, relative, and marginal. Lack of response

to treatment was defined a size reduction of <25%.<sup>[9]</sup> If there were no therapeutic response to shallomin, the patients would be referred for cryotherapy. In case of complete recovery of warts after the patients received the last dose of shallomin, they went through a follow-up period of 2–6 months to examine the reoccurrence of the wart.

## The method of calculating the sample size and the method of sampling

$$n = \frac{(Z_1 - \alpha/2 + Z_1 - \beta)^2 (P_1[1 - P_1] + P_2[1 - P_2])}{(P_1 - P_2)^2}$$

For a confidence level of 95%:  $Z_1 - \alpha/2 = 1.96$

For a power of 90%:  $Z_1 - \beta = 1.28$

$$P_1 = 0.9$$

$$P_2 = 0.6$$

$$P_1 - P_2 = 0.3$$

For each group:

$$n = \frac{(1.96 + 1.28)^2 (0.9(0.1) + 0.6(0.4))}{(0.9 - 0.6)^2} = 39$$

## The method of extracting from *Hirtifolium boiss* (shallomin)

About 300 white *Hirtifolium Boiss* was washed and then diced. The dices were immersed in 300 mL distilled water and stirred for 5 h using a magnetic stirrer. Whatman filter paper No. 1 was used to filter the mixture. The obtained blue extract and ethyl acetate were mixed at a proportion of 50:50 for 10 min and then, the mixture was centrifuged at 5000 rpm. The upper surface was separated with a funnel and was transferred to a clean Erlenmeyer flask after the ethyl estate layer was removed. This process was repeated three times, and the extracts were mixed and dried on a rotatory operator at the temperature of 50°C. The resulting material was weighed and dissolved in different densities of ethanol.

## Statistical analysis methods

Data analysis was first conducted using descriptive statistics including frequency distribution tables, graphs, and numerical values. Then, the relationship between qualitative and quantitative variables was examined through Chi-square test, Fisher's exact test, *t*-test or its nonparametric equivalent, i.e., Mann–Whitney, respectively. The significant level was set at 0.05 for all tests. Data analysis was conducted using IBM SPSS 16.0 (New York).

## Results

The mean age of the study sample was  $16.47 \pm 2.16$  years; 70% ( $n = 28$ ) of them were below 20 years, and 30% ( $n = 12$ ) were over 30 years. The mean appearance time of plane warts

was  $4.27 \pm 5$  months. Among the patients, 82.5% ( $n = 33$ ) had an appearance time of below 6 months and 17.5% ( $n = 7$ ) had an appearance time of over 6 months. Half of the warts were treated with cryotherapy one every 2 weeks and the rest with shallomin twice a week for 8 weeks, and they were examined five times at the beginning, 2, 4, 6, and 8 weeks after the treatment regarding therapeutic criteria (decrease in wart size, reduction in the number of warts).

During the five sessions, mean  $\pm$  standard deviation of wart size (in cm) was  $0.98 \pm 0.07$ ,  $0.43 \pm 0.28$ ,  $0.17 \pm 0.22$ , and 0 (in the 6<sup>th</sup> week after treatment with cryotherapy), respectively. Treatment with cryotherapy was significantly effective in reducing the size of the warts ( $P < 0.0001$ ). During the five sessions, mean  $\pm$  standard deviation of the number of warts treated with cryotherapy was respectively  $3.9 \pm 1.95$ ,  $1.9 \pm 1.48$ ,  $0.75 \pm 1.14$ ,  $0.02 \pm 0.15$ , and 0 which indicates that cryotherapy could significantly decrease the number of the warts ( $P < 0.0001$ ) [Table 1].

Mean  $\pm$  standard deviation of size variable in warts treated with shallomin during the five sessions was  $0.96 \pm 0.13$ ,  $0.95 \pm 0.13$ ,  $0.88 \pm 0.20$ , and  $0.86 \pm 0.21$ , respectively. Comparing the mean size of the warts in the first session (2 weeks after the beginning of the treatment) and those of the fourth and fifth sessions (6 and 8 sessions after the treatment, respectively) indicated that there was a significant difference (in terms of the warts' size) between them ( $P$  values were 0.005 and 0.002, respectively). Mean  $\pm$  standard deviation of number variable in warts treated with shallomin during the five sessions was stably  $4.42 \pm 2.54$ , which means that shallomin had no effect on the number of warts [Table 2].

According to the results presented in Table 1, cryotherapy led to a reduction of from  $0.98 \pm 0.07$ -0 in the size of warts while shallomin only caused a decrease of 0.1 cm in the mean size of warts. Therefore, the statistical comparison of the two therapeutic methods indicates that shallomin had no effect on the number and size of warts while cryotherapy led to a significant decrease in the size of warts [Table 3].

Mean  $\pm$  standard deviation of size variable in warts treated with cryotherapy in the age group of  $<20$  years was respectively  $0.98 \pm 0.09$ ,  $0.49 \pm 0.23$ ,  $0.19 \pm 0.23$ , and 0, and in the group over 20 years was 1,  $0.29 \pm 0.33$ ,  $0.10 \pm 0.20$ , and 0, respectively. Mean  $\pm$  standard deviation of size variable in warts treated with shallomin in the age group of below 20 years was respectively  $0.94 \pm 0.15$ ,  $0.94 \pm 0.15$ ,  $0.94 \pm 0.15$ ,  $0.85 \pm 0.22$ , and  $0.83 \pm 0.23$ , and in the group over 20 years was 1, 1,  $0.97 \pm 0.08$ ,  $0.93 \pm 0.16$ , and  $0.91 \pm 0.16$ , respectively. Comparing the means showed that compared to cryotherapy, shallomin caused no significant reduction in the size of warts in different age groups [Table 4].

**Table 1: The effect of cryotherapy on the warts during the five sessions**

Pairwise comparison (measure: measure-1)						
s.c (I)	s.c (J)	Mean difference (I-J)	SE	Significant	95% CI for difference <sup>b</sup>	
					Lower bound	Upper bound
1	2	0.555*	0.045	0.000	0.463	0.647
	3	0.818*	0.038	0.000	0.741	0.894
	4	0.988*	0.013	0.000	0.962	1.013
	5	0.988*	0.013	0.000	0.962	1.013
2	1	-0.555*	0.045	0.000	-0.647	-0.463
	3	0.263*	0.047	0.000	0.167	0.358
	4	0.433*	0.045	0.000	0.342	0.523
	5	0.433*	0.045	0.000	0.342	0.523
3	1	-0.818*	0.038	0.000	-0.894	-0.741
	2	-0.263*	0.047	0.000	-0.358	-0.167
	4	0.170*	0.036	0.000	0.097	0.243
	5	0.170*	0.036	0.000	0.097	0.243
4	1	-0.988*	0.013	0.000	-1.013	-0.962
	2	-0.433*	0.045	0.000	-0.523	-0.342
	3	-0.170*	0.036	0.000	-0.243	-0.097
	5	0.000	0.000		0.000	0.000
5	1	-0.988*	0.013	0.000	-1.013	-0.962
	2	-0.433*	0.045	0.000	-0.523	-0.342
	3	-0.170*	0.036	0.000	-0.243	-0.097
	4	0.000	0.000		0.000	0.000

SE: Standard error, CI: Confidence interval, S.C: Size of cryo

**Table 2: The effect of shallomin on the warts during the five sessions**

Pairwise comparisons (measure: measure-1)						
s.sh (I)	s.sh (J)	Mean difference (I-J)	SE	Significant	95% CI for difference <sup>b</sup>	
					Lower bound	Upper bound
1	2	0.000	0.000		0.000	0.000
	3	0.007	0.007	0.323	-0.008	0.023
	4	0.082*	0.028	0.005 <sup>b</sup>	0.026	0.139
	5	0.102*	0.030	0.002 <sup>b</sup>	0.041	0.164
2	1	0.000	0.000		0.000	0.000
	3	0.007	0.007	0.323	-0.008	0.023
	4	0.082*	0.028	0.005 <sup>b</sup>	0.026	0.139
	5	0.102*	0.030	0.002 <sup>b</sup>	0.041	0.164
3	1	-0.007	0.007	0.323	-0.023	0.008
	2	-0.007	0.007	0.323	-0.023	0.008
	4	0.075*	0.027	0.009 <sup>b</sup>	0.020	0.130
	5	0.095*	0.030	0.003 <sup>b</sup>	0.034	0.156
4	1	-0.082*	0.028	0.005 <sup>b</sup>	-0.139	-0.026
	2	-0.082*	0.028	0.005 <sup>b</sup>	-0.139	-0.026
	3	-0.075*	0.027	0.009 <sup>b</sup>	-0.130	-0.020
	5	0.020	0.010	0.058 <sup>b</sup>	-0.001	0.041
5	1	-0.102*	0.030	0.002 <sup>b</sup>	-0.164	-0.041
	2	-0.102*	0.030	0.002 <sup>b</sup>	-0.164	-0.041
	3	-0.095*	0.030	0.003 <sup>b</sup>	-0.156	-0.034
	4	-0.020	0.010	0.058 <sup>b</sup>	-0.041	0.001

<sup>b</sup>> 0.05, SE: Standard error, CI: Confidence interval, S.Sh: Size of shallomin

**Table 3: Comparing the effectiveness of shallomin and cryotherapy on the size of the warts during the five separate sessions followed by the treatment**

Paired samples test								
	Paired differences					<i>t</i>	df	Significant (2-tailed)
	Mean±SD	SE mean	95% CI of the difference					
			Lower	Upper				
Pair 1	0.02500	0.11036	0.01745	−0.01030	0.06030	1.433	39	0.160
Pair 2	−0.53000	0.33220	0.05253	−0.63624	−0.42376	−10.090	39	0.000
Pair 3	−0.78500	0.24237	0.03832	−0.86251	−0.70749	−20.484	39	0.000
Pair 4	−0.88000	0.20531	0.03246	−0.94566	−0.81434	−27.108	39	0.000
Pair 5	−0.86000	0.21579	0.03412	−0.92901	−0.79099	−25.206	39	0.000

SD: Standard deviation, SE: Standard error, CI: Confidence interval

**Table 4: Comparing the effect of shallomin and cryotherapy on reducing the size of the warts according to the age groups**

Paired samples test									
Age average	Pair type	Paired differences					t	df	Significant (2-tailed)
		Mean	SD	SE mean	95% CI of the difference				
					Lower	Upper			
<20	Pair 1	0.03571	0.13113	0.02478	−0.01513	0.08656	1.441	27	0.161
	Pair 2	−0.45357	0.30609	0.05785	−0.57226	−0.33488	−7.841	27	0.000
	Pair 3	−0.75000	0.25166	0.04756	−0.84758	−0.65242	−15.770	27	0.000
	Pair 4	−0.85714	0.22015	0.04160	−0.94251	−0.77178	−20.602	27	0.000
	Pair 5	−0.83571	0.23288	0.04401	−0.92602	−0.74541	−18.989	27	0.000
≥20	Pair 2	−0.70833	0.33428	0.09650	−0.92072	−0.49594	−7.340	11	0.000
	Pair 3	−0.86667	0.20597	0.05946	−0.99753	−0.73580	−14.576	11	0.000
	Pair 4	−0.93333	0.16143	0.04660	−1.03590	−0.83076	−20.028	11	0.000
	Pair 5	−0.91667	0.16422	0.04741	−1.02101	−0.81232	−19.336	11	0.000

SD: Standard deviation, SE: Standard error, CI: Confidence interval

## Discussion and Conclusion

Warts can appear differently depending on the involved epithelial tissue and the type of HPV. Skin manifestation due to HPV infections includes common warts (*verruca vulgaris*), plantar warts (*verruca plantaris*), plane warts (*verruca plana*), and anogenital warts (*condylomata acuminata*). The victims are mostly among the age group of 12–16 years. According to the results of the previously conducted studies, although warts disappear after 2 years in 40% individuals, in some cases, they spread and become bigger over time and resists different treatments (Kilkenny and Marks, 1996).<sup>[13]</sup> Treating warts has always been a medical challenge for doctors, and since no sole treatment has been proved effective, various therapeutic methods have been introduced to deal with this disease. In this study, the effects of shallomin and cryotherapy on treating warts were compared in a randomized clinical trial which consisted of 4 patients with plane warts. In previous studies, the antibacterial effect of shallomin on Gram-positive and Gram-negative pathogenic bacteria with a minimum inhibitory concentration (MIC) of 20–5 µg/ml and the antifungal effect in the form of fungus ball and fungistatic with a MIC of 0.15–20 µg/ml (MIC) have been reported.<sup>[14]</sup> On the other hand, in their clinical trial, Pipelzadeh *et al.*<sup>[12]</sup> observed that the topical

lotion of shallomin 0.5% was effective in treating oral herpes and preventing their progress. Therefore, it seems that in addition to its extensive antibacterial and antifungal effect, shallomin can have antiviral effects. In the present study, the therapeutic response of plane warts to shallomin and cryotherapy was considered as size reduction of warts and in clinical terms and divided into the four categories of complete (75%–100% disappearance of the warts), relative (50%–75% reduction of the warts), marginal (25%–49% reduction of the warts), and no response (<25% reduction of the warts). Regarding the therapeutic response, the results of the study indicated that shallomin caused a significant reduction in the size of warts 6–8 weeks after the treatment ( $P = 0.002$ , confidence interval = 0.041–0.164). Since the mean size of the wart at the beginning of the treatment was  $0.96 \pm 0.13$  cm and reached  $0.86 \pm 0.07$  cm 8 weeks after treatment with shallomin (a size reduction of <25%), the therapeutic response is classified as no response. On the contrary, cryotherapy led to a complete therapeutic response, such that it reduced the size of warts from  $0.98 \pm 0.07$  cm in the 1<sup>st</sup> week to 0 in the 6<sup>th</sup> week ( $P < 0.0001$ ). According to the results of the present study, it can be stated that shallomin cannot be proposed as a probable (common) therapy for warts, in comparison with cryotherapy. Moreover, shallomin had no effect on reducing the number of warts while cryotherapy led to a significant decrease in the number of the skin lesions

from  $3.9 \pm 1.95$  in the first session to 0 in the fifth ( $P < 0.0001$ ). According to the results of the current study that is the first and the only research focusing on the effect of shallomin on treating plane warts, it can be stated that despite of its antibacterial, antifungal, and antiherpetic properties, shallomin cannot be an effective clinical treatment for plane warts.

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### Conflicts of interest

There are no conflicts of interest.

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